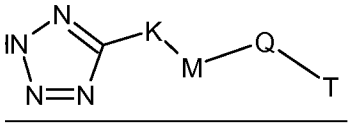
AMENDMENTS TO THE CLAIMS

The following Listing of Claims replaces all prior versions, and listings, of claims.

LISTING OF CLAIMS

1. (Currently Amended) A pharmaceutical composition comprising: insulin and a zinc-binding ligand which reversibly binds to a His^{B10} Zn^{2+} site of an insulin hexamer, wherein the ligand is



wherein K is a valence bond, C_1-C_6-alkylene, -NH-C(=O)-U-, -C_1-C_6-alkyl-S-, -C_1-C_6-alkyl-O-, -C(=O)-, or -C(=O)-NH-, wherein any C_1-C_6-alkyl moiety is optionally substituted with R^{38},

U is a valence bond, C_1-C_6-alkenylene, -C_1-C_6-alkyl-O- or C_1-C_6-alkylene wherein any C_1-C_6-alkyl moiety is optionally substituted with C_1-C_6-alkyl,

R^{38} is C_1-C_6-alkyl, aryl, wherein the alkyl or aryl moieties are optionally substituted with one or more substituents independently selected from R^{39},

R^{39} is independently selected from halogen, cyano, nitro, amino,

M is is indolylene optionally substituted with one or more substituents independently selected from R^{40},

R^{40} is selected from: hydrogen, halogen, -CN, -CH_2CN, -CHF_2, -CF_3, -OCF_3, -$OCHF_2$, -OCH_2CF_3, -OCF_2CHF_2, -$S(O)_2CF_3$, -$OS(O)_2CF_3$, -SCF_3, -NO_2, -OR^{41}, -$NR^{41}R^{42}$, -SR^{41}, -$NR^{41}S(O)_2R^{42}$, -$S(O)_2NR^{41}R^{42}$, -$S(O)NR^{41}R^{42}$, -$S(O)R^{41}$, -$S(O)_2R^{41}$, -$OS(O)_2R^{41}$, -$C(O)NR^{41}R^{42}$, -$OC(O)NR^{41}R^{42}$, -$NR^{41}C(O)R^{42}$, -$CH_2C(O)NR^{41}R^{42}$, -OC_1-C_6-alkyl-$C(O)NR^{41}R^{42}$, -CH_2OR^{41}, -$CH_2OC(O)R^{41}$, -$CH_2NR^{41}R^{42}$, -$OC(O)R^{41}$, -OC_1-C_6-alkyl-$C(O)OR^{41}$, -OC_1-C_6-alkyl-OR^{41}, -S-C_1-C_6-alkyl-$C(O)OR^{41}$, –C_2-C_6-alkenyl-$C(=O)OR^{41}$, -NR^{41}-C(=O)-C_1-C_6-alkyl-$C(=O)OR^{41}$, -NR^{41}-C(=O)-C_1-C_6-alkenyl-$C(=O)OR^{41}$, -$C(O)OR^{41}$, –C_2-C_6-alkenyl-$C(=O)R^{41}$, =O, -NH-C(=O)-O-C_1-C_6-alkyl, or -NH-C(=O)-C(=O)-O-C_1-C_6-alkyl; C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl, which may each optionally be substituted with one or more substituents selected from R^{43}; aryl, aryloxy, aryloxycarbonyl, aroyl, arylsulfanyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, aryl-C_2-

C_6-alkenyl, aroyl-C_2-C_6-alkenyl, aryl-C_2-C_6-alkynyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, heteroaryl-C_2-C_6-alkenyl or heteroaryl-C_2-C_6-alkynyl, wherein the cyclic moieties optionally may be substituted with one or more substituents selected from R^{44},

R^{41} and R^{42} are independently selected from hydrogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkenyl, aryl-C_1-C_6-alkyl or aryl, wherein the alkyl moieties may optionally be substituted with one or more substituents independently selected from R^{45}, and the aryl moieties may optionally be substituted with one or more substituents independently selected from R^{46}; R^{41} and R^{42} when attached to the same nitrogen atom may form a 3 to 8 membered heterocyclic ring with the said nitrogen atom, the heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulphur, and optionally containing one or two double bonds,

R^{43} is independently selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-OR^{41}$, and $-NR^{41}R^{42}$

R^{44} is independently selected from halogen, $-C(O)OR^{41}$, $-CH_2C(O)OR^{41}$, $-CH_2OR^{41}$, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{41}$, $-NR^{41}R^{42}$ and C_1-C_6-alkyl,

R^{45} is independently selected from halogen, -CN, $-CF_3$, $-OCF_3$, -O-C_1-C_6-alkyl, -C(O)-O-C_1-C_6-alkyl, -COOH and $–NH_2$,

R^{46} is independently selected from halogen, $-C(O)OC_1$-C_6-alkyl, -COOH, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, -OH, $-OC_1$-C_6-alkyl, $-NH_2$, C(=O) or C_1-C_6-alkyl,

Q is a valence bond, C_1-C_6-alkylene, -C_1-C_6-alkyl-O-, -C_1-C_6-alkyl-NH-, -NH-C_1-C_6-alkyl, -NH-C(=O)-, -C(=O)-NH-, -O-C_1-C_6-alkyl, -C(=O)-, or -C_1-C_6-alkyl-C(=O)-N(R^{47})- wherein the alkyl moieties are optionally substituted with one or more substituents independently selected from R^{48},

R^{47} and R^{48} are independently selected from hydrogen, C_1-C_6-alkyl, aryl optionally substituted with one or more R^{49},

R^{49} is independently selected from halogen and –COOH,

T is: hydrogen; C_1-C_6-alkyl, C_2-C_6-alkenyl , C_2-C_6-alkynyl, C_1-C_6-alkyloxy-carbonyl, wherein the alkyl, alkenyl and alkynyl moieties are optionally substituted with one or more substituents independently selected from R^{50}; aryl, aryloxy, aryloxy-carbonyl, aryl-C_1-C_6-alkyl, aroyl, aryl-C_1-C_6-alkoxy, aryl-C_2-C_6-alkenyl, aryl-C_2-C_6-alkyny-, heteroaryl, heteroaryl-C_1-C_6-alkyl, heteroaryl-C_2-C_6-alkenyl, heteroaryl-C_2-C_6-alkynyl, wherein any alkyl, alkenyl , alkynyl, aryl and heteroaryl moiety is optionally substituted with one or more substituents independently selected

from R^{50},

R^{50} is C_1-C_6-alkyl, C_1-C_6-alkoxy, aryl, aryloxy, aryl-C_1-C_6-alkoxy, -C(=O)-NH-C_1-C_6-alkyl-aryl, -C(=O)-NR^{50A}-C_1-C_6-alkyl, -C(=O)-NH-$(CH_2CH_2O)_m$$C_1$-$C_6$-alkyl-COOH, heteroaryl, heteroaryl-C_1-C_6-alkoxy, -C_1-C_6-alkyl-COOH, -O-C_1-C_6-alkyl-COOH, -$S(O)_2R^{51}$, -C_2-C_6-alkenyl-COOH, -OR^{51}, -NO_2, halogen, -COOH, -CF_3, -CN, =O, -$N(R^{51}R^{52})$, wherein m is 1, 2, 3 or 4, and wherein the aryl or heteroaryl moieties are optionally substituted with one or more R^{53}, and the alkyl moieties are optionally substituted with one or more R^{50B},

R^{50A} and R^{50B} are independently selected from -C(O)OC_1-C_6-alkyl, -COOH, -C_1-C_6-alkyl-C(O)OC_1-C_6-alkyl, -C_1-C_6-alkyl-COOH, or C_1-C_6-alkyl,

R^{51} and R^{52} are independently selected from hydrogen and C_1-C_6-alkyl,

R^{53} is independently selected from C_1-C_6-alkyl, C_1-C_6-alkoxy, -C_1-C_6-alkyl-COOH, -C_2-C_6-alkenyl-COOH, -OR^{51}, -NO_2, halogen, -COOH, -CF_3, -CN, or -$N(R^{51}R^{52})$,

or any enantiomer, diastereomer, racemic mixture, tautomer, or salt thereof with a pharmaceutically acceptable acid or base.

~~selected from the group consisting of: benzotriazoles, 3-hydroxy 2-naphthoic acids, salicylic acids, tetrazoles, thiazolidinediones, 5-mercaptotetrazoles, pyrimidinetriones, or 4-cyano-1,2,3-triazoles, or enantiomers, diastereomers, racemic mixtures, tautomers, or salts thereof with a pharmaceutically acceptable acid or base.~~

2. – 127. (Cancelled).

128. (Original) A pharmaceutical composition according to claim 127 wherein K is a valence bond, C_1-C_6-alkylene, -NH-C(=O)-U-, -C_1-C_6-alkyl-S-, -C_1-C_6-alkyl-O-, or -C(=O)-, wherein any C_1-C_6-alkyl moiety is optionally substituted with R^{38}.

129. (Original) A pharmaceutical composition according to claim 128 wherein K is a valence bond, C_1-C_6-alkylene, -NH-C(=O)-U-, -C_1-C_6-alkyl-S-, or -C_1-C_6-alkyl-O, wherein any C_1-C_6-alkyl moiety is optionally substituted with R^{38}.

130. (Original) A pharmaceutical composition according to claim 129 wherein K is a

valence bond, C_1-C_6-alkylene, or -NH-C(=O)-U, wherein any C_1-C_6-alkyl moiety is optionally substituted with R^{38}.

131. (Original) A pharmaceutical composition according to claim 130 wherein K is a valence bond or C_1-C_6-alkylene, wherein any C_1-C_6-alkyl moiety is optionally substituted with R^{38}.

132. (Original) A pharmaceutical composition according to claim 130 wherein K is a valence bond or -NH-C(=O)-U.

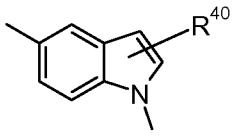
133. (Original) A pharmaceutical composition according to claim 131 wherein K is a valence bond.

134. (Original) A pharmaceutical composition according to claim 127 wherein U is a valence bond or -C_1-C_6-alkyl-O-.

135. (Original) A pharmaceutical composition according to claim 134 wherein U is a valence bond.

136. – 141. (Cancelled).

142. (Original) A pharmaceutical composition according to claim 141 wherein M is



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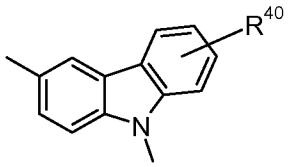
143. (Original) A pharmaceutical composition according to claim 139 wherein M is carbazolylene optionally substituted with one or more substituents independently selected from R^{40}.

144. (Original) A pharmaceutical composition according to claim 143 wherein M is



145. (Currently Amended) A pharmaceutical composition according to claim 1~~27~~ wherein R^{40} is selected from: hydrogen, halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{41}$, $-NR^{41}R^{42}$, $-SR^{41}$, $-S(O)_2R^{41}$, $-NR^{41}C(O)R^{42}$, $-OC_1$-C_6-alkyl-$C(O)NR^{41}R^{42}$, $-C_2$-C_6-alkenyl-$C(=O)OR^{41}$, $-C(O)OR^{41}$, =O, -NH-C(=O)-O-C_1-C_6-alkyl, or -NH-C(=O)-C(=O)-O-C_1-C_6-alkyl, C_1-C_6-alkyl or C_2-C_6- alkenyl which may each optionally be substituted with one or more substituents independently selected from R^{43}, aryl, aryloxy, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, aryl-C_2-C_6-alkenyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, or heteroaryl-C_2-C_6-alkenyl, wherein the cyclic moieties optionally may be substituted with one or more substituents selected from R^{44}.

146. (Previously Amended) A pharmaceutical composition according to claim 145 wherein R^{40} is selected from: hydrogen, halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{41}$, $-NR^{41}R^{42}$, $-SR^{41}$, $-S(O)_2R^{41}$, $-NR^{41}C(O)R^{42}$, $-OC_1$-C_6-alkyl-$C(O)NR^{41}R^{42}$, $-C_2$-C_6-alkenyl-$C(=O)OR^{41}$, $-C(O)OR^{41}$, =O, -NH-C(=O)-O-C_1-C_6-alkyl, or -NH-C(=O)-C(=O)-O-C_1-C_6-alkyl, C_1-C_6-alkyl or C_2-C_6- alkenyl which may each optionally be substituted with one or more substituents independently selected from R^{43}, ArG1, ArG1-O-, ArG1-C_1-C_6-alkoxy, ArG1-C_1-C_6-alkyl, ArG1-C_2-C_6-alkenyl, Het3, Het3-C_1-C_6-alkyl, or Het3-C_2-C_6-alkenyl, wherein the cyclic moieties optionally may be substituted with one or more substituents selected from R^{44}.

147. (Previously Amended) A pharmaceutical composition according to claim 146 wherein R^{40} is selected from: hydrogen, halogen, $-CF_3$, $-NO_2$, $-OR^{41}$, $-NR^{41}R^{42}$, $-C(O)OR^{41}$, =O, or $-NR^{41}C(O)R^{42}$, C_1-C_6-alkyl, and ArG1.

148. (Original) A pharmaceutical composition according to claim 147 wherein R^{40} is hydrogen.

149. (Previously Amended) A pharmaceutical composition according to claim 147 wherein R^{40} is selected from: Halogen, $-NO_2$, $-OR^{41}$, $-NR^{41}R^{42}$, $-C(O)OR^{41}$, or $-NR^{41}C(O)R^{42}$, Methyl, and Phenyl.

150. (Original) A pharmaceutical composition according to claim 127 wherein R^{41} and R^{42} are independently selected from hydrogen, C_1-C_6-alkyl, or aryl, wherein the aryl moieties may optionally be substituted with halogen or –COOH.

151. (Original) A pharmaceutical composition according to claim 150 wherein R^{41} and R^{42} are independently selected from hydrogen, methyl, ethyl, or phenyl, wherein the phenyl moieties may optionally be substituted with halogen or –COOH.

152. (Original) A pharmaceutical composition according to claim 127 wherein Q is a valence bond, C_1-C_6-alkylene, -C_1-C_6-alkyl-O-, -C_1-C_6-alkyl-NH-, -NH-C_1-C_6-alkyl, -NH-C(=O)-, -C(=O)-NH-, -O-C_1-C_6-alkyl, -C(=O)-, or -C_1-C_6-alkyl-C(=O)-N(R^{47})- wherein the alkyl moieties are optionally substituted with one or more substituents independently selected from R^{48}.

153. (Original) A pharmaceutical composition according to claim 152 wherein Q is a valence bond, $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-CH_2-CH_2-O-$, $-CH_2-NH-$, $-CH_2-CH_2-NH-$, $-NH-CH_2-$, $-NH-CH_2-CH_2-$, -NH-C(=O)-, -C(=O)-NH-, $-O-CH_2-$, $-O-CH_2-CH_2-$, or -C(=O)-.

154. (Original) A pharmaceutical composition according to claim 127 wherein R^{47} and R^{48} are independently selected from hydrogen, methyl and phenyl.

155. (Previously Amended) A pharmaceutical composition according to claim 127 wherein T is: Hydrogen, C_1-C_6-alkyl optionally substituted with one or more substituents independently selected from R^{50}, aryl, aryl-C_1-C_6-alkyl, heteroaryl, wherein the alkyl, aryl and heteroaryl moieties are optionally substituted with one or more substituents independently selected from R^{50}.

156. (Previously Amended) A pharmaceutical composition according to claim 155 wherein T is: hydrogen, C_1-C_6-alkyl optionally substituted with one or more substituents independently selected from R^{50}, ArG1, ArG1-C_1-C_6-alkyl, Het3, wherein the alkyl, aryl and heteroaryl moieties are optionally substituted with one or more substituents independently selected from R^{50}.

157. (Previously Amended) A pharmaceutical composition according to claim 156 wherein T is: hydrogen, C_1-C_6-alkyl, optionally substituted with one or more substituents independently selected from R^{50}, phenyl, phenyl-C_1-C_6-alkyl, wherein the alkyl and phenyl moieties are optionally substituted with one or more substituents independently selected from R^{50}.

158. (Original) A pharmaceutical composition according to claim 157 wherein T is phenyl substituted with R^{50}.

159. (Original) A pharmaceutical composition according to claim 127 wherein R^{50} is C_1-C_6-alkyl, C_1-C_6-alkoxy, aryl, aryloxy, aryl-C_1-C_6-alkoxy, -C(=O)-NH-C_1-C_6-alkyl-aryl, -C(=O)-NR^{50A}-C_1-C_6-alkyl, -C(=O)-NH-$(CH_2CH_2O)_m$$C_1$-$C_6$-alkyl-COOH, heteroaryl, -C_1-C_6-alkyl-COOH, -O-C_1-C_6-alkyl-COOH, -$S(O)_2R^{51}$, -C_2-C_6-alkenyl-COOH, -OR^{51}, -NO_2, halogen, -COOH, -CF_3, -CN, =O, -$N(R^{51}R^{52})$, wherein the aryl or heteroaryl moieties are optionally substituted with one or more R^{53}.

160. (Original) A pharmaceutical composition according to claim 159 wherein R^{50} is C_1-C_6-alkyl, C_1-C_6-alkoxy, aryl, aryloxy, -C(=O)-NR^{50A}-C_1-C_6-alkyl, -C(=O)-NH-$(CH_2CH_2O)_m$$C_1$-$C_6$-alkyl-COOH, aryl-$C_1$-$C_6$-alkoxy , -$OR^{51}$, -$NO_2$, halogen, -COOH, -$CF_3$, wherein any aryl moiety is optionally substituted with one or more R^{53}.

161. (Original) A pharmaceutical composition according to claim 160 wherein R^{50} is C_1-C_6-alkyl, aryloxy, -C(=O)-NR^{50A}-C_1-C_6-alkyl, -C(=O)-NH-$(CH_2CH_2O)_m$$C_1$-$C_6$-alkyl-COOH, aryl-$C_1$-$C_6$-alkoxy , -$OR^{51}$, halogen, -COOH, -$CF_3$, wherein any aryl moiety is optionally substituted with one or more R^{53}.

162. (Original) A pharmaceutical composition according to claim 161 wherein R^{50} is C_1-C_6-alkyl, ArG1-O-, -C(=O)-NR^{50A}-C_1-C_6-alkyl, -C(=O)-NH-$(CH_2CH_2O)_mC_1$-C_6-alkyl-COOH, ArG1-C_1-C_6-alkoxy , -OR^{51}, halogen, -COOH, -CF_3, wherein any aryl moiety is optionally substituted with one or more R^{53}.

163. (Original) A pharmaceutical composition according to claim 162 wherein R^{50} is -C(=O)-$NR^{50A}CH_2$, -C(=O)-NH-$(CH_2CH_2O)_2CH_2$l-COOH, or -C(=O)-$NR^{50A}CH_2CH_2$.

164. (Original) A pharmaceutical composition according to claim 162 wherein R^{50} is phenyl, methyl or ethyl.

165. (Original) A pharmaceutical composition according to claim 164 wherein R^{50} is methyl or ethyl.

166. (Currently Amended) A pharmaceutical composition according to claim 1~~27~~ wherein m is 1 or 2.

167. (Currently Amended) A pharmaceutical composition according to claim 1~~27~~ wherein R^{51} is methyl.

168. (Currently Amended) A pharmaceutical composition according to claim 1~~27~~ wherein R^{53} is C_1-C_6-alkyl, C_1-C_6-alkoxy, -OR^{51}, halogen,or -CF_3.

169. (Currently Amended) A pharmaceutical composition according to claim 1~~27~~ wherein R^{50A} is -C(O)OCH_3, -C(O)OCH_2CH_3 -COOH, -CH_2C(O)OCH_3, -CH_2C(O)OCH_2CH_3, -CH_2CH_2C(O)OCH_3, -CH_2CH_2C(O)OCH_2CH_3, -CH_2COOH, methyl, or ethyl.

170. (Currently Amended) A pharmaceutical composition according to claim 1~~27~~ wherein R^{50B} is -C(O)OCH_3, -C(O)OCH_2CH_3 -COOH, -CH_2C(O)OCH_3, -CH_2C(O)OCH_2CH_3,

-$CH_2CH_2C(O)OCH_3$, -$CH_2CH_2C(O)OCH_2CH_3$, -CH_2COOH, methyl, or ethyl.

171. – 204. (Cancelled)

205. (Original) A pharmaceutical composition according to claim 1 wherein the insulin is rapid acting insulin.

206. (Original) A pharmaceutical composition according to claim 1 wherein the insulin is selected from the group consisting of human insulin, an analogue thereof, a derivative thereof, and combinations of any of these.

207. (Original) A pharmaceutical composition according to claim 206 wherein the insulin is an analogue of human insulin selected from the group consisting of

i. An analogue wherein position B28 is Asp, Lys, Leu, Val, or Ala and position B29 is Lys or Pro; and

ii. des(B28-B30), des(B27) or des(B30) human insulin.

208. (Original) A pharmaceutical composition according to claim 207, wherein the insulin is an analogue of human insulin wherein position B28 is Asp or Lys, and position B29 is Lys or Pro.

209. (Original) A pharmaceutical composition according to claim 207 wherein the insulin is des(B30) human insulin.

210. (Original) A pharmaceutical composition according to claim 207 wherein the insulin is is an analogue of human insulin wherein position B3 is Lys and position B29 is Glu or Asp.

211. (Original) A pharmaceutical composition according to claim 206 wherein the insulin is a derivative of human insulin having one or more lipophilic substituents.

212. (Original) A pharmaceutical composition according to claim 211 wherein the insulin derivative is selected from the group consisting of B29-N^{ε}-myristoyl-des(B30) human insulin, B29-N^{ε}-palmitoyl-des(B30) human insulin, B29-N^{ε}-myristoyl human insulin, B29-N^{ε}-palmitoyl human insulin, B28-N^{ε}-myristoyl Lys^{B28} Pro^{B29} human insulin, B28-N^{ε}-palmitoyl Lys^{B28} Pro^{B29} human insulin, B30-N^{ε}-myristoyl-$Thr^{B29}Lys^{B30}$ human insulin, B30-N^{ε}-palmitoyl-$Thr^{B29}Lys^{B30}$ human insulin, B29-N^{ε}-(N-palmitoyl-γ-glutamyl)-des(B30) human insulin, B29-N^{ε}-(N-lithocholyl-γ-glutamyl)-des(B30) human insulin, B29-N^{ε}-(ω-carboxyheptadecanoyl)-des(B30) human insulin and B29-N^{ε}-(ω-carboxyheptadecanoyl) human insulin.

213. (Original) A pharmaceutical composition according to claim 212 wherein the insulin derivative is B29-N^{ε}-myristoyl-des(B30) human insulin.

214. (Original) A pharmaceutical composition according to claim 1 comprising 2-6 moles $zinc^{2+}$ ions per mole insulin.

215. (Original) A pharmaceutical composition according to claim 214 comprising 2-3 moles $zinc^{2+}$ ions per mole insulin.

216. (Original) A pharmaceutical composition according to claim 1 further comprising at least 3 molecules of a phenolic compound per insulin hexamer.

217. (Original) A pharmaceutical composition according to claim 1 further comprising an isotonicity agent.

218. (Original) A pharmaceutical composition according to claim 1 further comprising a buffer substance.

219. – 220. (Cancelled).